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WO 02/05839 A1

(54) Title: AGENT FOR INHIBITING ADHESION OF THE PATHOGENIC FLORA OF THE SKIN

(57) Abstract: The invention relates to the use of a casein derivative for the preparation of a composition for cosmetic, pharmaceutical or veterinary use, intended to be administered to humans or to animals for the purpose of preventing or treating disorders induced by the pathogens of the cutaneous system.

Agent for inhibiting adhesion of the pathogenic flora of the skin

The subject of the present invention is the use of casein derivatives for the preparation of compositions for cosmetic, pharmaceutical or veterinary use intended for stabilizing and/or regulating the cutaneous ecosystem in mammals. The invention also relates to compositions containing such an agent.

State of the art

The proliferation of pathogens such as *Staphylococcus aureus*, *Streptococcus pyogenes* or *Propionibacterium acnes*, or of some yeasts such as *Candida albicans*, can cause dysregulation of the cutaneous system or even more serious disorders in the skin or the mucous membranes such as eczema, candidiasis, dermatitis, and the like.

Numerous means of treatment against these pathogenic agents are known. Antibiotics or chemical antibacterial agents and antifungals are the most conventionally used. Alternatively, topical disinfectants of the aldehyde type are chosen.

Thus, published patent application FR 2740039 describes the use of a substance chosen from aldehydes and bifunctional compounds, preferably glutaraldehyde, for inhibiting the attachment of pathogenic strains such as *Staphylococcus aureus* to the keratinocytes and corneocytes.

Also, hexachlorophene and its derivatives are known as antibacterial substances and are more particularly used against *Propionibacterium acnes*. These treatments are in general expensive and harmful both to health and to the environment.

Alternative, nontoxic treatments are also known which consist in using the antifungal, bactericidal or bacteriostatic properties of certain strains of microorganisms.

Thus, application EP 99204489 describes the use of strains of *Lactobacillus*, *Micrococcus* or *Bifidobacterium* selected for their adhesion capacity with respect to skin cells and their competitive properties with respect to the adhesion of the pathogens of the cutaneous system, to prepare cosmetic compositions capable of stabilizing and regulating the pathogenic flora of the skin.

Also, application PCT/EP96/00441 describes sugars and their derivatives as antiadhesion active agents for the treatment of yeast and dermatophyte mycoses.

The invention is intended to find a novel natural nonbacterial agent capable of controlling and regulating the cutaneous ecosystem.

Summary of the invention

Thus, the present invention relates to the use of a casein derivative for the preparation of a composition for cosmetic, pharmaceutical or veterinary use, intended to be administered to humans or to animals for the purpose of preventing or treating disorders induced by the pathogens of the cutaneous system.

Indeed, it has been observed, surprisingly, that casein derivatives were capable of stabilizing and/or regulating the pathogenic flora of the cutaneous system by inhibiting the adhesion of pathogens such as *Streptococcus pyogenes*, *Trichophyton rubrum*, *Pityrosporum ovale*, *M. furfur* or *Candida albicans*, for example.

The casein derivative may be chosen from the group comprising caseinoglycomacropeptide (CGMP), the glycosylated derivatives of

caseinoglycomacropeptides and the active products obtained by hydrolysis of caseinoglycomacropeptide or their derivatives.

Caseinoglycomacropeptides (CGMPs) may be used in any form, and in particular in the form of calcium or sodium salts, for example.

The present invention also relates to a composition for cosmetic, pharmaceutical or veterinary use, containing at least one casein derivative capable of stabilizing and/or regulating the pathogenic flora of the cutaneous system.

This composition may be in particular in the form of a cream, lotion, dermatological cake, shampoo or powder, for example.

The quantity of CGMPs contained in the composition may be from 0.01% to 10% by weight, and preferably from 0.5% to 5% by weight of the dry matter content.

The composition according to the invention is intended in particular for the therapeutic or prophylactic treatment of healthy, sensitive and/or diseased skins and/or mucous membranes which may exhibit disorders of the cutaneous system such as those induced by pathogens such as *Streptococcus pyogenes*, *Trichophyton rubrum*, *Pityrosporum ovale* or *Candida albicans*, for example.

Detailed description of the invention

The name "cutaneous system" covers all the cells of the skin (i.e. keratinocytes) but also the corneocytes.

According to a first object, the present invention proposes the use of casein derivatives for the preparation of a composition for cosmetic, pharmaceutical or veterinary use, intended to be administered to humans or to animals for the

purpose of preventing or treating disorders induced by pathogens of the cutaneous system.

The casein derivative may be caseinoglycomacropeptide (CGMP), a glycosylated derivative of caseinoglycomacropeptide or an active product obtained by hydrolysis of caseinoglycomacropeptide or of its derivative.

Indeed, it has been observed, surprisingly, that casein derivatives and in particular caseinoglycomacropeptides (CGMPs) and their derivatives had the capacity to adhere to cutaneous cells, to stabilize and to regulate the pathogenic bacterial flora of the cutaneous system, in particular by inhibiting the adhesion of pathogens such as *Streptococcus pyogenes*, *Trichophyton rubrum*, *Pityrosporum ovale*, *Candida albicans*, *M. furfur*, for example.

The cutaneous disorders induced by these pathogens may be in particular atopic dermatitis (in the remission phases as maintenance treatment), acne, candidiasis, seborrhoeic dermatitis, Pityriasis versicolor, impetigo or eczematous superinfections (Table 1).

Pathogens	Dermatological information
Streptococcus pyogenes	Impetigo, eczema and herpes superinfected
Candida albicans	Candidiasis
Pityrosporum ovale	Seborrhoeic dermatitis, Pityriasis versicolor
Trichophyton rubrum	Onychomycosis, dermatophytosis
M. furfur	Varied

Table 1: Dermatological disorders caused by pathogens of the cutaneous system

Disorders of the cutaneous system may also be linked to therapeutic treatments with antibiotics, with antimycotics, to diabetes (candidiasis), to a pathological condition of the mucous membranes (vaginal candidiasis), to chronic

eczema (homeostasis disequilibrium), to sensitive skins (premature babies, children), greasy skins (linked to hormonal dysregulations which may promote the establishment of bacteria) or to dandruff states.

According to a preferred embodiment of the invention, the CGMPs may be used in the form of sodium or calcium salts, for example. It is also possible to use their derivatives, in particular their glycosylated (e.g. sialylated) derivatives or the active products of their hydrolysis.

The casein derivative may be used at concentrations ranging from 0.01 to 10%, and preferably from 0.5 to 5%.

CGMP, which is a sialylated macropeptide formed by the action of rennet or of chymosin on milk kappa-caseins, is preferably used. To prepare CGMP, it is possible to use an ion-exchange method of treating a whey raw material, for example as described in PCT 98/53702 which comprises the following steps: where appropriate, adjusting the pH of the liquid whey raw material to a value of 1 to 4.3, bringing the said liquid into contact with a predominantly weak anionic resin in alkaline form until a stabilized pH of 4.5-5.5 is obtained, and then separating the resin and the liquid whey product which is recovered, and desorbing the CGMP from the resin.

As whey raw material, there may be used any product or by-product containing CGMP, and for example:

- the sweet whey obtained after separation of casein coagulated with rennet,
- a sweet whey or such a whey which has demineralized to a greater or lesser degree for example by electrodialysis, ion-exchange, reverse osmosis, electrodeionization or a combination of these methods,
- a concentrate of sweet whey,

- a concentrate of sweet whey which has been demineralized to a greater or lesser degree for example by electrodialysis, ion-exchange, reverse osmosis, electrodeionization or a combination of these methods,
- a concentrate of substantially lactose-free sweet whey proteins obtained for example by ultrafiltration followed by diafiltration,
- lactose crystallization mother liquors from a sweet whey,
- a sweet whey ultrafiltration permeate,
- the product of hydrolysis, by a protease, of a native casein obtained by acid precipitation of skimmed milk by an inorganic acid or by biological acidification, where appropriate with addition of calcium ions,
- the product of hydrolysis of a caseinate by a protease.

According to another object, the present invention relates to a composition for cosmetic, pharmaceutical or veterinary use, containing at least one casein derivative capable of stabilizing and/or regulating the pathogen flora of the cutaneous system.

The casein derivative may be caseinoglycomacropeptide (CGMP), a glycosylated derivative of caseinoglycomacropeptide or an active product obtained by hydrolysis of caseinoglycomacropeptide or of its derivative.

To prepare such a composition, the casein derivative is incorporated into a pharmaceutically or cosmetically acceptable carrier, in a quantity varying according to the desired application. It may be present at from 0.01 to 10% relative to the total weight of the composition, preferably from 0.5 to 5%.

The compositions according to the invention may be administered by the topical or ocular route.

By the topical route, the pharmaceutical compositions based on compounds according to the invention are preferably intended for the treatment of

the skin and of the mucous membranes and may be provided in the form of ointments, creams, milks, pomades, powders, impregnated pads, solutions, gels, sprays, lotions or suspensions. They may also be provided in the form of microspheres or nanospheres or lipid or polymeric vesicles or polymeric patches or hydrogels allowing controlled release. These compositions for topical administration may be provided either in anhydrous form or in aqueous form depending on the clinical indication.

By the ocular route, they are mainly collyria.

The present invention relates more particularly to a cosmetic composition containing, in a cosmetically acceptable carrier, at least one casein derivative as defined above. The cosmetic composition may contain CGMP in an amount of at least 0.01% by weight relative to the total weight of the composition, and preferably from 0.5 to 5%.

This cosmetic composition is in particular intended for body and hair hygiene. It may be provided in particular in the form of a cream, a milk, a lotion, a gel, lipid or polymeric microspheres or nanospheres or vesicles, a soap or a shampoo.

In the compositions according to the invention, the casein derivative may be combined with retinoids or corticosteroids, or combined with anti-free radical agents, with α-hydroxy or α-keto acids or their derivatives, or with ion-channel blockers.

The pharmaceutical and cosmetic compositions according to the invention may, in addition, contain inert or even pharmacodynamically or cosmetically active additives or combinations of these additives and in particular: wetting agents; depigmenting agents such as hydroquinone, azelaic acid, caffeic acid or kojic acid; emollients; moisturizing agents such as glycerol, PEG-400, thiamorpholinone and its derivatives or urea; antiseborrhoeic or anti-acne agents,

such as S-carboxymethylcysteine, S-benzylcysteamine, their salts and their derivatives, or benzoyl peroxide; antibiotics such as erythromycin and its esters, neomycin, clindamycin and its esters, tetracyclines; antifungal agents such as ketoconazole or 4,5-polymethylene-3-isothiazolinones; agents promoting hair regrowth, such as Minoxidil (2,4-diamino-6-piperidinopyrimidine-3-oxide) and its derivatives, Diazoxide (7-chloro-3-methyl-1,2,4-benzothiadiazine 1,1-dioxide) and Phenytoïn (5,4-diphenyl-2,4-imidazolidinedione); nonsteroidal anti-inflammatory agents; carotenoids and, in particular, β-carotene; antipsoriatic agents such as anthralin and its derivatives and finally 5,8,11,14-eicosatetraynoic and 5,8,11-eicosatrynoic acids, their esters and amides.

The composition according to the invention may also contain preservatives such as esters of para-hydroxybenzoic acid, stabilizing agents, moisture-regulating agents, pH-regulating agents, osmotic pressure-modifying agents, emulsifying agents, UV-A and UV-B screening agents, antioxidants such as α-tocopherol, butylated hydroxyanisole or butylated hydroxytoluene.

The composition according to the invention is intended in particular for therapeutic or prophylactic treatment of healthy, sensitive and/or diseased skins and/or mucous membranes which may exhibit disorders of the cutaneous system such as in particular:

- infectious complications such as superinfected atopic dermatitis, impetiginized eczema, ulcer, wounds, burns, superinfected inflammatory acne,
- polydermatites such as impetigo, superficial folliculites,
- seborrhoeic dermatites, Pityriasis versicolor
- dermatophytoses (Tinea capitis, Tinea corporis, athlete's foot, Hebra's eczema marginatum, Tinea circinata)
- candidiases (vaginal, interdigital, linked to risky professions or to diabetes)
- disorders linked to therapeutic treatments with antibiotics or with antimycotics,

- disorders caused by hormonal dysregulations (greasy skins) or dandruff states
- sensitive skins (premature babies, children).

The present invention finally relates to a composition for veterinary or cosmetic use for animals, containing at least one casein derivative having the properties described above. Such a composition may be provided in the form of dry or liquid shampoos, powders, mousses or lotions for example. It may contain up to 10% CGMPs, for example.

The composition for veterinary use is intended for the treatment or prevention of infections caused by ectoparasites, dysfunctions due to streptococcal infections (due to *S. pyogenes*) and mycotic infections (candidiases due to *C. albicans* and pityrosporoses due to *P. canis*).

The veterinary composition may have anti-inflammatory, antiitching or antidandruff properties.

The present invention is described in greater detail below with the aid of the examples which are given by way of illustration of the subject of the invention and which do not constitute in any manner a limitation thereto. The percentages are given by weight unless otherwise stated.

Examples

Example 1: Preparation of CGMP and of As-CGMP

A sweet bovine whey is used which is concentrated beforehand to 17% dry matter content, and then demineralized by electrodialysis, decationized on a column of strong cationic resin, deanionized on a column of weak anionic resin and spray-dried in a drying tower, having the composition indicated below:

Proteins (CGMP included)	11.7%
Lactose	81.7%
Ash	1%
Lipids	1%
Water	balance for 100

This demineralized whey powder is solubilized in deionized water and the solution has an initial pH of 3.8. In the above installation, 392 kg of this solution are treated at the temperature of 8°C by stirring it in the reactor in the presence of 23 kg of weak anionic resin (IMAC HP 661®, Rohm & Haas regenerated in OH^- form) for 4 h.

The stabilization of the pH at 4.89 indicates the end of the reaction. The liquid is then drawn off and the resin is recovered as above. After concentrating the liquid to 28% dry matter content by evaporation, the concentrate is spray-dried in a drying tower.

An analysis of the concentrate by HPLC shows that the reaction removed 89% of the initial CGMP. Moreover, the powder contains 9.1% of whey proteins, which corresponds to a yield of 90% of whey proteins.

To recover the CGMP, the resin is successively washed with deionized water, with 30 l of a 0.5% aqueous HCl solution and with 30 l of deionized water, and then the CGMP is eluted with twice 40 l of a 2% aqueous NaOH solution and rinsed with 30 l of deionized water. After having combined the eluate and rinsing volumes, the whole is concentrated to a volume of 25 l by ultrafiltration with a membrane having a nominal cutoff of 3000 daltons, and then the retentate is freeze-dried and 900 g of CGMP are obtained, which corresponds to a yield of 80% relative to the initial CGMP.

The Asialo-CGMP (As-CGMP) is obtained by enzymatic or chemical desialylation, as described by Neeser J.R. et al., 1988, *Infect. Immun.*, **56**, 3201-3208.

Example 2: Tests *in vitro* for inhibiting the adhesion of *Streptococcus pyogenes*, *Trichophyton rubrum* and *Candida albicans* with the casein derivatives CGMP and As-CGMP.

The *in vitro* adhesion model is based on the incubation of a radiolabelled and standardized suspension of a pathogenic cutaneous microorganism with a monolayer of immortalized human keratinocytes (HaCaT line, Boukamp P. *et al., J. Cell Biol.*, **106**, 761-771, 1988).

The inhibitory activity of CGMP in relation to this adhesion is evaluated in the context of a coincubation with the monolayer of the pathogen and of the compound to be tested by assaying the radioactivity retained on the monolayer.

Keratinocytes

The HaCaT cells are cultured in DMEM medium supplemented with 10% foetal calf serum, at 37°C under 5% CO_2. They are inoculated in a 6-well cluster at the rate of 1.0E+04 cells/cm^2. The adhesion trial is carried out 5 days after confluence. The monolayers are washed 3 times with PBS before incubation with the microorganisms.

Microorganisms

The pathogens *Streptococcus pyogenes*, *Trichophyton rubrum* and *Candida albicans* are cultured in broth by subculturing from a slope culture according to standard procedures which are specific to them. An OD/bacterial density relationship was established for each of the microorganisms tested, on the basis of the serial dilutions and the counts on agar medium.

Radiolabelling

The radiolabelling of the microbial strains is obtained by incorporating 100 µCi/10 ml of ^{3}H-adenine for 24 h of culture into TCS broth. The suspension is then centrifuged for 10 minutes at 3000 rpm and washed 3 times in PBS. The cell density is adjusted with PBS buffer to about 2.0E+08 cfu/ml (OD at 525 nm = 0.5). The specific radioactivity is determined by scintillation counting on 100 µl of the suspension.

Adhesion assay:

1 ml of the radiolabelled microbial suspension is incubated for 1 h at 35°C. The monolayer is washed 3 times with PBS buffer and lysed by addition of 1 N NaOH for 30 minutes at room temperature. The lysate is transferred to a scintillation flask and incubated for 1 h at 60°C with 1 ml of hyamine hydroxide (Carlo Erba, ref. 464951). The ^{3}H activity is counted in a liquid scintillation counter. Each assay is repeated in triplicate. A control for adhesion to the plastic support is also carried out.

Adhesion is defined as the ratio of the radioactivity adhered to the radioactivity introduced, multiplied by 100.

Adhesion inhibition assay

The solutions of casein derivatives are prepared in PBS. The concentrations tested cover the range 0-10 mg/ml. The configuration tested consists in simultaneously incubating the radiolabelled pathogen and the derivative on the monolayer.

The results are given in Tables 2, 3 and 4.

Table 2: Inhibition of the adhesion of *S. pyogenes* to HaCaT cells by various concentrations of CGMP and As-CGMP.

Concen-trations	Inhibition of *S. pyogenes* adhesion (%)					
	1 mg/ml	2 mg/ml	3 mg/ml	5 mg/ml	8 mg/ml	10 mg/ml
CGMP	34	45	52	55	58	60
As-CGMP	15	27	35	52	60	65

Table 3: Dose/effect of CGMP on the adhesion of *S. pyogenes, C. albicans* to the keratinocytes HaCaT in culture.

CGMP concentration	Adhesion (%)					
	0 mg/ml	1 mg/ml	2 mg/ml	5 mg/ml	7 mg/ml	10 mg/ml
S. pyogenes	100	77	43	37	30	23
C. albicans	100	68	61.5	61.5	58	52

Table 4: Dose/effect of CGMP on the adhesion of *T. rubrum* to the keratinocytes HaCaT in culture.

CGMP concentration	Spores/100 keratinocytes					
	0 mg/ml	1 mg/ml	2 mg/ml	5 mg/ml	7 mg/ml	10 mg/ml
T. rubrum	88	87	86	68	40	1

CGMP and As-CGMP have the capacity to inhibit the adhesion of pathogens such as *Streptococcus pyogenes, Trichophyton rubrum, Candida albicans*, for example. They can thus stabilize or regulate the pathogenic bacterial flora of the cutaneous system.

Example 3: Tests ex vivo for inhibition of the adhesion of *M. furfur* by CGMP.

Materials and methods

Animals: 15 SKH female mice, 7 to 8 weeks old and weighing about 30 g, were provided by C. River. 5 mice were used for each group testing a different topical application.

Preparation of the inoculum

A suspension of *M. furfur* is prepared for its inoculation in mice. For that, a slope preculture of strain 1 is carried out on a solid medium (AES, AEB 122 859) at 35°C for 18 to 24 h. After incubation, the bacterium is resuspended in 10 ml of sterile saline solution and then recovered after centrifugation at 3000 rpm for 10 min. The supernatant is then removed and the pellet is taken up in 10 ml of saline solution. This procedure is repeated twice. An inoculum suspension is prepared by resuspending the bacteria washed in 4 ml of sterile saline solution. The OD at 525 nm is adjusted to about 0.14. It contains about 10^8 cfu/ml.

Inoculation of the mice

The skin of the mice is delipidized on the flanks with 95% ethanol (Merck). 50 µl of a suspension containing a 50/50 mixture of the inoculum 1.0E+07 cfu/ml and of the product to be tested (CGMP in solution at 1%, 2%, 3% and 5%) were slowly applied with the aid of a micropipette over the delipidized area (6.25 cm^2). The inoculated sites are protected by occlusion for 1 h under a sterile plastic dressing (Dermafilm 33 × 15, ref. 38.3015, Vygon laboratory).

Counting of the viable bacteria in the lesions

4 hours after the application of the suspension, the mice are killed under anaesthesia with forene (Abbott France). The inoculated sites are excised as a block (diameter 12 mm). The skin biopsies removed are ground and homogenized in 2 ml

of sterile saline solution with a Polytron (PT 2100, Bioblock Scientific) (5 rpm, 5 min).

A 1 ml sample of homogenized tissue is added to 9 ml of a sterile saline solution and 0.1 ml of this mixture is cultured on medium No. 110 using the 10-fold dilution method. After incubating for 48 hours at 35°C, the colonies developed are counted and the CFU (colony forming units) are determined.

Results

The results are presented in Table 5.

Table 5: Adhesion of *M. furfur* in the presence of various concentrations of CGMP.

CGMP concentration in solution	Adhesion (% of the control)				
	Control	1%	2%	3%	5%
M. furfur	100	32	22	16	15

Example 4: Body lotion

A body lotion is prepared which has the following composition: 8.0% mineral oil, 5.0% isopropyl palmitate, 2.0% polyglyceryl-3 diisostearate, 4.0% octyldodecanol, 0.3% carbomer, 0.2% sodium cocoylglutamate, 1.2% sodium hydroxide at 10%, a preservative, perfume, 0.5 to 5% CGMP as prepared in Example 1. The mixture is adjusted to 100% with water.

The body lotion thus obtained, by virtue of its antiadhesion properties against pathogens, is intended to stabilize and/or to regulate the pathogenic skin flora.

Example 5: Shampoo

A shampoo is prepared which has the following composition: 7% sodium lauryl sulphate, 2% cocamidopropylbetain, 2% sodium lauryl sulphonosuccinate, sodium chloride, preservative, perfume and 3% CGMP as prepared in Example 1. Their mixture is adjusted to 100% with water.

The shampoo thus prepared has properties which regulate the pathogenic scalp flora. It is in particular indicated in the treatment of dandruff states.

Example 6: Pharmaceutical composition

To obtain a pharmaceutical composition having properties which regulate the pathogenic skin flora, the fatty and aqueous phases having the following composition are prepared:

	CGMP as prepared in Example 1	1%
Fatty phase:	Arachidyl behenyl alcohol/arachidylglucoside	3%
	Isohexadecane	7%
	Sweet almond oil	3%
	Shea butter	2%
	B.H.T.	0.05%
	Propyl POB	0.05%
Aqueous phase:	Water	qs 100%
	Glycerin	5%
	Methyl POB	0.1%

The fatty and aqueous phases are heated to 75°C. Emulsification is then carried out by adding the aqueous phase to the fatty phase with stirring using a Rayneri device at 1000 rpm. 30 minutes after the emulsification, the mixture is homogenized for 1 minute using a Polytron (speed 4-5).

Example 7: Pharmaceutical composition

A composition is prepared in the same manner as in Example 6, but having the following composition:

	CGMP as prepared in Example 1	1%
Fatty phase:	glyceryl stearate and PEG 100 stearate	5%
	Isohexadecane	8%
	Shea butter	5%
	B.H.T.	0.05%
	DC 1503	1%
Aqueous phase:	Water	qs 100%
	Glycerin	3%
	Carbopol 981	0.2%
	Lubrajel	5%
	Phenoxyethanol	1%
	Sodium hydroxide	qs pH 6

Example 8: Shampoo for animals

A shampoo for animals is prepared which has the following composition: 5% sodium lauryl sulphate, 2% cocamidopropylbetain, 2% sodium lauryl sulphonosuccinate, 2% sodium chloride, 1.5% PEG-7 Glyceryl Cocoate, 0.75% propylene glycol, panthenol, glycerin, disodium phosphate, preservative, perfume and 2% CGMP as prepared in Example 1. The mixture is adjusted to 100% with water.

The shampoo thus prepared has properties which regulate the pathogenic flora of the cutaneous system of animals.

CLAIMS

1. Use of a casein derivative for the preparation of a composition for cosmetic, pharmaceutical or veterinary use, intended to be administered to humans or to animals for the purpose of preventing or treating disorders induced by the pathogens of the cutaneous system.

2. Use according to Claim 1, in which the casein derivative is capable of stabilizing and/or regulating the pathogenic flora of the cutaneous system by inhibiting the adhesion of pathogens such as *Streptococcus pyogenes*, *Trichophyton rubrum*, *Pityrosporum ovale*, *Candida albicans* or *M. furfur*.

3. Use according to Claims 1 or 2, in which the casein derivative is caseinoglycomacropeptide (CGMP), a glycosylate derivative of caseinoglycomacropeptide or an active product obtained by hydrolysis of caseinoglycomacropeptide or its derivative.

4. Use according to one of Claims 1 to 3, in which the casein derivative is used in an amount of 0.01 to 10% by weight.

5. Composition for cosmetic, pharmaceutical or veterinary use containing at least one casein derivative capable of stabilizing and/or regulating the pathogenic flora of the cutaneous system.

6. Composition according to Claim 5, in which the casein derivative is caseinoglycomacropeptide (CGMP), a glycosylate derivative of caseinoglycomacropeptide or an active product obtained by hydrolysis of caseinoglycomacropeptide or its derivative.

7. Composition according to Claims 5 or 6, containing from 0.01% to 10% by weight of the casein derivative.

8. Composition according to one of Claims 5 to 7, intended for the therapeutic or prophylactic treatment of skins and/or mucous membranes which may exhibit disorders of the cutaneous system such as those induced by pathogens such as *Streptococcus pyogenes*, *Trichophyton rubrum*, *Pityrosporum ovale*, *Candida albicans* or *M. furfur*.

9. Composition according to one of Claims 5 to 8, in which the disorders of the cutaneous system are:

- infectious complications such as superinfected atopic dermatitis, impetiginized eczema, ulcer, wounds, burns, superinfected inflammatory acne,
- polydermatites such as impetigo, superficial folliculites,
- seborrhoeic dermatites, Pityriasis versicolor
- dermatophytoses
- candidiases
- those linked to therapeutic treatments with antibiotics or with antimycotics,
- those caused by hormonal dysregulations or dandruff states.

10. Composition for veterinary use according to one of Claims 5 to 9, intended for the treatment or prevention of dysfunctions linked to streptococcal and mycotic infections in animals.

INTERNATIONAL SEARCH REPORT

Int. ...nal Application No
PCT/EP 01/07293

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K38/17 A61K7/48 A61P17/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, WPI Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 952 560 A (K. KIGASAWA ET AL.) 28 August 1990 (1990-08-28) claim 1; examples 17,31	1
X	US 4 007 264 A (A. QUEUILLE ET AL.) 8 February 1977 (1977-02-08) column 7, line 53 -column 8, line 41; claim 1; example 1	1,2,5,8
X	FR 8 087 M (J. MORELLE ET AL.) 20 July 1970 (1970-07-20) the whole document	1,5
X	FR 2 496 465 A (M. HAUCK) 25 June 1982 (1982-06-25) page 2, line 34 -page 3, line 4; claims 1,4; example 1	1

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
26 November 2001	12/12/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Glikman, J-F

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